Design and synthesis of a halogenated dibenzoxazepine library to probe antibiotic adjuvant activity

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Introduction

The gram-positive pathogen methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious risk to human health. In 2005 alone, there were 368,600 recorded cases of MRSA within hospitals in the United States.[1] In recent work we described the repotentiation of MRSA to oxacillin by the dibenzoxazepine anti-depressant amoxapine **(Figure 1)**.[2] Further investigations into this class of molecules identified the importance of aromatic halogenation for adjuvant activity. Thus, we sought to create a library of dibenzoxazepine analogs to probe the identity and location of aromatic substituents and evaluate their affect on adjuvant activity.

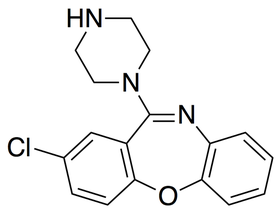


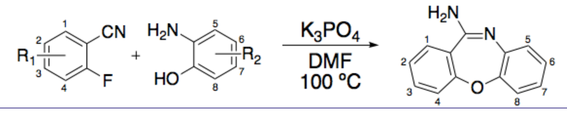
Figure 1. Amoxapine

Methods

Dibenzoxazepine derivatives were synthesized through a simple base-mediated condensation reaction.[3] We also explored acylation of the extracyclic amine as it presented a convenient and accessible handle for further functionalization. Minimum inhibitory concentrations (MIC) of the derivatives against *S. aureus* (ATCC 43300, MRSA) were determined for several compounds.[4] Antibiotic repotentiation assays were performed similarly to the MIC assays, with cultures being treated with sub-inhibitory concentrations of compound before the addition of antibiotics.

Results

Table 1. Synthesized compounds and their corresponding functional groups



Compound	R_1	R_2	% yield
1	2 – Cl	H	76
2	4 – Cl	H	39
3	3 – Cl	H	44
4	1 – Cl	H	12
5	H	7 – Cl	13
6	H	6 – Cl	12
7	2 – F	H	<1
8	2 – I	H	79
9	1 – Br	H	3
10	H	H	57
11	H	5, 6 - Naphthalene	11
12	2 – OCH_3	H	N/A

Table 2. MIC of compounds against MRSA (43300)

Compound	Compound Concentration (mM)	MIC (μM)
1	100	>200
2	100	>200
3	100	>200
13	100	>200

Table 3. Antibiotic resensitization in MRSA (43300)

Compound	Compound Concentration (mM)	Oxacillin MIC (mg/mL)	Fold Reduction
Oxacillin	-	16	-
1	100	32	0.5
2	100	16	1
3	100	32	0.5
13	100	32	0.5

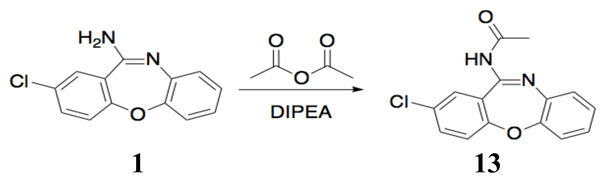


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Figure 2. Acylation of the extracyclic amine

Discussion & Future Directions

Thirteen dibenzoxazepine derivatives were synthesized and purified **(Table 1, Figure 2).** Four compounds have been fully characterized and assayed for biological activity thus far. None of the tested compounds possessed any antibiotic activity, nor did they repotentiate MRSA to oxacillin **(Tables 2 & 3).** We hypothesize that the additional polarity or hydrogen bonding of the extracyclic amine as compared to amoxapine may affect activity. We will explore additional modifications of the extracyclic amine to identify derivatives with restored adjuvant activity. This will allow us to return to our study of aromatic substituents and their effect on antibiotic adjuvant activity.

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References

1. Elixhauser, Anne; Steiner, Claudia, Infections with Methicillin-Resistant Staypholococcus Aureus (MRSA) in U.S. Hospitals, 1993-2005. *HCUP Statistical Brief #35* **2007**.
2. Wilson, TJ; Blackledge, MS; Viguiera, PA, Resensitization of methicillin-resistant Staphylococcus aureus by amoxapine, an FDA approved antidepressant. *Heliyon* **2018**, 4.
3. Feng, Jiang-Bo; Wu, Xiao-Feng, Base-promoted synthesis of dibenzoxazepinamines and quinazoliniines under metal-free conditions. *Green Chemistry* **2015**. 17, 4522-4526.
4. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement.* CLSI document M100-S25. Wayne, PA: Clinical and Laboratory Standards Institute; **2015**.